How the hat fits: Structural biology study reveals shape of epigenetic enzyme complex

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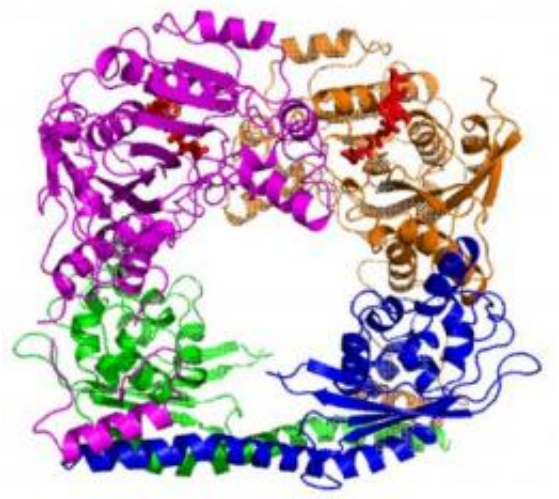

Histone acetyltransferases (HATs) are enzymes that can epigenetically modify gene regulation. Just how they modify their targets depends on the shape they form. This ring structure is formed by two Rtt109 HATs (purple and gold) and two Vsp75 "chaperones" (blue and green), which are proteins that guide the enzymes to their target by, in part, dictating the size of the hole formed when they make a ring. As the HAT settles atop its target (a histone protein) the shape of the ring complex determines which part of the target gets modified. Other chaperones may help Rtt109 modify other parts of its target protein. Credit: Ronen Marmostein, Ph.D./The Wistar Institute

a field that describes how genes may be regulated without altering the underlying DNA itself—scientists are deciphering the many ways in which enzymes act on the proteins surrounding DNA within cells.

One type of these enzymes, proteins known as histone acetyltransferases (HATs), act on DNA by modifying DNA-bound proteins called histones. This act of modification, called acetlyation, can dictate how histones interact with DNA and other proteins affecting processes such as DNA replication, transcription (reading the gene), and repair. In the February 9 issue of the journal *Structure*, available online, researchers at The Wistar Institute are the first to describe the complete atomic structure formed by a yeast HAT, known as Rtt109, and one of its associated proteins. Their findings demonstrate how a particular histone acetylation event works, a crucial step to understanding epigenetics and the related processes that underlie both health and disease.

According to the study's senior author, Ronen Marmorstein, Ph.D., professor and program leader of Wistar's Gene Expression and Regulation Program, two copies of Rtt109 bind to two copies of a "chaperone" protein to form a ring.

"The ring fits atop a histone much like a halo, and we find that the type of chaperone dictates exactly how the enzyme affects the histone by determining the exact position of acetylation," said Marmorstein. "The structure represents a nice model system for the regulation of protein acetylation, and teaches us something new about the biology of this enzyme, Rtt109."

The act of acetylation adds an "acetyl group," a small chemical structure, to a lysine—one of the amino acids that make up a given protein. Altering one lysine could change the shape of a protein, such as a histone, in a subtle way, perhaps redirecting how it functions. Rtt109, the researchers say, acetylates any of three specific lysines on histones, and exactly which of the histone lysines are modified is determined by which chaperone escorts Rtt109 into place. Since histones are such crucial DNA-associated proteins, altering a single lysine in a single part of the structure can have profound effects on the "behavior" of that histone,

such as exposing a particular set of genes to be read, for example.

In the paper, Marmorstein and his colleagues show how Rtt109 associates with a particular chaperone called Vps75. Rtt109 also associates with another chaperone, Asf1, which has been shown to enable the Rtt109 to modify lysines in a different spot on a given histone, creating a different effect in how that histone interacts with DNA and in turn changing the cell's biological properties.

Their study is the first to show that two Rtt109 enzymes pair up with two Vps75 chaperones to form a ring. The laboratory created crystals of the protein complex and used a technique called X-ray crystallography to "see" the structure of the complex by analyzing the patterns formed when X-rays bounce off the crystals. They used the powerful X-ray source at the Argonne National Laboratory's Advanced Photon Source, which enabled the team to determine the structure of the protein complex at the atomic scale—at a resolution of 2.8 angstroms (2.8 billionths of a meter), which is smaller than the distance between individual rungs on the DNA ladder.

Since the Marmorstein laboratory began its work on HATs over a decade ago, several large-scale studies have shown that acetylation occurs to over 2000 proteins, not just histones. According to Marmorstein, it appears there is an entire web of communication going on within cells directly attributable to protein acetylation, another level of complexity in an already-complex field.

"We have seen many different proteins over several different pathways become affected by acetylation, which can alter the processes of RNA metabolism, cell cycle control, cancer, and a number of different aspects of life. It looks like protein acetylation has much broader biological implications than initially appreciated," said Marmorstein.

"In many ways, it seems a lot like what we have seen in recent years with protein kinases and cell signaling," said Marmorstein. "What we're learning is that these HATs, and possibly other protein acetyltransferases, are regulated in much the same way. They have these profound effects within cells, but it is still very new to science. How it works is a big black box that we intend to decipher."

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